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| EXAMINER | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/583,191 | KROGER ET AL. | |
| | Examiner | Art Unit | |
| | MARIA LEAVITT | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2 and 6-19* is/are pending in the application.

4a) Of the above claim(s) *1 and 8-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 6 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01-29-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

***Detailed Action***

Applicant's response to the restriction requirements of 04-09-2009 has been entered.

Claim status. Claims 1, 2 and 6-19 are currently pending. Applicant's election **without traverse** of Group II, drawn to a method of regulating the expression of a gene comprising introducing into a host cell an expression unit comprising SEQ ID Nos. 1 and 2, i.e., claim 2, and product claims 6 and 7, drawn to an expression unit comprising SEQ ID No. 1 and SEQ ID No. 2, in Applicants' response filed on 04-09-2009 is acknowledged. Claims 1, 6 and 8-17 have been amended, and claims 5, 20-48, 51, 52 and 54 have been cancelled by Applicants' amendment of 04-09-2009.

Accordingly, claims 1, 8-19 are withdrawn for further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

Therefore claims 2, 6 and 7 are examined on the merits to which the following grounds of rejection are applicable.

***Priority***

The present application is a 35 U.S.C. 371 national stage filing of International Application No. PCT/EP2004/014337, filed December 16, 2004, which claims priority to German Application No. 10359660.7, filed December 18, 2003. Fining of a certified untranslated copy of the German Application No. 10359660.7, filed December 18, 2003 is acknowledged.

***Information Disclosure Statement***

The information disclosure statements filed on January 29, 2008 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copies. The following reference has been considered to the extent that an English abstract is provided: DE-4440118.

All other documents in said Information Disclosure statement were considered as noted by the Examiner initials in the copy attached hereto.

***Specification objection***

The Specification is objected because of the following informalities:

At page 2, lines 14-18, the specification recites, "In the literature (E. coli and S. typhimurium, Neidhardt F. C. 1995 ASM Press) it is reported that both the composition of the polynucleotide sequence of the Shine-Dalgarno sequence, the sequence string of the bases, but also the distance of a polynucleotide sequence present in the Shine-Dalgarno sequence from has a considerable influence on the translation initiation rate". This sentence is grammatically incorrect. Appropriate correction is required.

***35 USC 101-non-statutory subject matter***

35 U.S.C. §101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 6 and 7 are rejected under 35 USC §101 because the claimed invention is directed to non-statutory subject matter.

Claim 6 recites the term "an expression unit comprising a nucleic acid molecule having promoter activity". The specification as filed at page 10, lines 20-25, provides a definition of "an

expression unit" as "a nucleic acid having expression activity, i.e. a nucleic acid which, in functional linkage to a nucleic acid to be expressed, or gene, regulates the expression, i.e. the transcription and the translation of this nucleic acid or of this gene". As written, 6 and 7 do not sufficiently distinguish over cells on their own right that exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. SEQ. ID. NO. 1 represents the promoter sequence of superoxide dismutase (Psod) from wild type *Corynebacterium glutamicum*. Thus the claim is broadly reading on a *Corynebacterium glutamicum* comprising the endogenous sodA gene comprising a sodA gene able to express the *Corynebacterium melassecola* manganese-cofactored superoxide dismutase . In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified" as taught at Example 1, of the specification. See MPEP 2105.
Corrected by Anne Marie to SEQ Appl. 10/492911.

***Claim Rejections - 35 USC § 112- Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 2, 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6, at lines 11-13, is indefinite in its recitation of "wherein the nucleic acid molecule does not consist of SEQ ID NO: 1". Claim 6 step A) recites "a nucleic acid molecule comprising the nucleotide sequence of SEQ ID No. 1 which is broadly interpreted as a nucleic acid molecule comprising the full length of SEQ ID No. 1, with or without additional nucleotides at either or both ends. Hence, the recitation of claim 6, comprising the nucleic acid molecule of SEQ ID No. 1 which simultaneously, at step D), lacks the nucleic acid molecule of SEQ ID No. 1 appears to be contradictory. How can an expression vector comprise both the SEQ ID No. 1 while " does not consist of SEQ ID No. 1" (step D of claim 6)? The metes and bounds are not clearly set forth.

Likewise, claim 7, at lines 10-11, is indefinite in its recitation of "with the proviso that the nucleic acid having the sequence SEQ ID No. 2 is excluded. Claim 7 step E) recites "a nucleic acid molecule comprising the nucleotide sequence of SEQ ID No. 2 which is broadly interpreted as a nucleic acid molecule comprising the full length of SEQ ID No. 2, with or without additional nucleotides at either or both ends. Hence, the recitation of claim 7, comprising the nucleic acid molecule of SEQ ID No. 2 which simultaneously, at step H), lacks the nucleic acid molecule of SEQ ID No. 2 appears to be of contradictory significance. How can an expression vector comprising SEQ ID No. 2 simultaneously lack SEQ ID No. 2 (step H of claim 7)? The metes and bounds are not clearly set forth.

In addition, it is unclear whether the claimed isolated nucleic acid molecules of claim 7 are comprised in the nucleic acid molecule having promoter activity which is functionally linked to a gene of interest for transcription/ translation or the isolated nucleic acid molecules of claim 7

are linked to the nucleotide of SEQ ID no. 1 in other ways e.g., as a conjugate product. The metes and bounds are not clearly set forth.

Moreover, claim 6 is indefinite in its recitation of "wherein the nucleic acid molecules is functionally linked to a nucleic acid sequence which ensures the translation of ribonucleic acids". As a promoter is a region of DNA that facilitates the transcription of a particular gene, it is unclear how a promoter ensures translation and not necessary transcription. The metes and bounds are not clearly set forth.

For the purpose of a compact prosecution, claims 6 has been interpreted as an expression vector comprising the full length of SEQ ID No. 1, with or without additional nucleotides at either or both ends (Claim 6, subpart A) or the full length of SEQ ID No. 1 or any portion (claim 6, steps B) –D) wherein said nucleic acid molecule is functionally linked to a gene of interest and ensures transcription/translation of ribonucleic acids . Similarly, claim 7 has been interpreted as an expression unit comprising the full length of SEQ ID No. 2 or any portion and the full length of SEQ ID No. 2, with or without additional nucleotides at either or both ends (Claim 7, subpart E) or the full length of SEQ ID No. 2 or any portion of said sequence (claim 7, steps F) –H).

***Claim Rejections - 35 USC § 112- First paragraph- Scope of Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising the full length promoter region of the *C. melassecola sodA* gene comprising the nucleotide sequences selected from the group consisting of SEQ ID NO: 1 or the complement thereof and SEQ ID NO: 2 or the complement thereof, does not reasonably provide enablement for a nucleotide sequence of at least 90% homology to SEQ ID NO. 1 or SEQ ID No. 2. Moreover, the specification does not provide sufficient guidance for either fragments or variants thereof capable of hybridizing to any of the nucleotide sequence selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims, when given the broadest possible interpretation, encompass a genus of fragments and/or variants of polynucleotides having 90% homology to a nucleotide sequence of

SEQ ID No. 1 and SEQ ID No. 2, embracing the full length or any portion of the sequences with the contemplated functionality of having promoter activity for expression of an heterologous enzyme of the biosynthesis pathways (p. 6, lines 20-40; p. 10, lines 20-25). In addition, claim 6 subparts (C) to (D) and claim 7 subpart (G) to (H), as written, broadly embrace a genus of fragment and/or variants that specifically hybridize to nucleic acid molecules comprising the nucleotide sequences of SEQ ID NO 1 and/or SEQ ID No. 2 with the contemplated functionality, of being used as a promoter for overexpression of the *Corynebacterium glutamicum* lysC gene or metA gene (p. 73, lines 15-16).

The specification provides insufficient data to enable claims directed to the fragments and/or variants of SEQ ID NO 1 and SEQ ID NO: 2 as broadly claimed. Thereby, specific issues including the functional limitations of DNA base sequences of 90% homology to of SEQ ID NO 1 and SEQ ID No. 2 or polynucleotide sequences of any undetermined length that specifically hybridize to nucleic acid molecule of SEQ ID NO 1 and SEQ ID NO: 2, broadly reading on a genus of functional DNA able to regulate the transcription rate or expression rate of an heterologous gene in a fermentation process (p. 16, lines 25-30) have to be examined and considered for patentability regarding the broadly claimed DNA base sequences.

The present invention is drawn to promoter regions associated with the sodA gene encoding the *Corynebacterium melassecola* manganese-cofactored superoxide dismutase (SOD) that has been found to be particularly effective for the expression of heterologous genes in C. glutamicum. The specification describes that the nucleic acid sequence SEQ. ID NO. 1 represents the promoter sequence of superoxide dismutase (Psod) from the wild type Corynebacterium glutamicum (p. 7, lines 10-13) whereas the nucleic acid sequence of SEQ. ID.

NO. 2 represents the nucleic acid sequence of the expression unit of superoxide dismutase (Psod) from *Corynebacterium glutamicum* (page 12, lines 25-27, page 14, lines 34-36). Specifically, the specification as filed teaches overexpression of the Lys C gene with aid of the heterologous expression unit Psod (SEQ. ID. NO. 2) (p. 73, lines 15-16; p. 76, Table 1; p. 78, Table 2a) and metA (p. 86, Table 3a). Moreover, the specification discloses at page 73, lines 26-30, and at page 84, lines 29-30, that the amplified DNA fragment from the sodA gene of *C. glutamicum* ATCC 13032 of approximately 620 base pairs in size (e.g., comprising SEQ ID Nos. 1 and 2 ) was used to generate the ATCC13032 Psod $lysC^{fbr}$ and ATCC 13032 pCLiK5MCS PSODmetA, respectively. Results on the effect of the Psod lysC construct on lysine production, evidence enhanced lysine production in strains ATCC13032 Psod $lysC^{fbr}$ in relation to ATCC13032 $lysC^{fbr}$ or control ATCC13032 (p. 78, Table 2a). Likewise, production of metA in strain ATCC 13032 pCLiK5MCS PSODmetA exhibits approximately a two-fold increase in relation to ATCC 13032 pCLiK5MCS PmetA metA. However, Applicant has provided little or no guidance beyond the mere enumeration of promoter regions associated with the sodA gene including the binding sites for RNA polymerase holoenzymes, also called -35 and -10 regions, and the binding site for ribosomal 16S RNA, also called ribosome binding site (p. 17 lines 15-30) and the amplified DNA fragment from the sodA gene of C. glutamicum ATCC 13032 of approximately 620 base pairs in size was used to generate the ATCC13032 Psod $lysC^{fbr}$ and ATCC 13032 pCLiK5MCS PSODmetA, to enable one of ordinary skill in the art to determine, without undue experimentation, positions of the 620 base of the Psod from *C. glutamicum* which are tolerant to changes (e.g. by nucleotide substitutions or deletions), and the nature and extent of changes that

can be made in these positions to retain the promoter improved activity of *C. glutamicum* cultured in MMA medium.

At the time the invention was made, Pátek et al., (2003, Journal of Biotechnology pages 311-323) discloses various sites or regions in *C. glutamicum* promoters sharing common sequence features including a conserved extended −10 region tgngnTA(c/t)aaTgg, with a −35 region less conserved (Abstract). Moreover, Pátek et al., teaches that the 53 *C. glutamicum* promoters were active in the exponential growth phase in a complete medium, and all of them are recognized by the primary sigma factor (coded by the *sigA* gene) responsible for directing the RNA polymerase to promoters of vegetative (house-keeping) genes (page 314, col. 1, paragragph 1 ). Moreover, the author states that on the basis of the analysis of promoters "it is possible to foresee the probable position of the −10 hexamer of the promoter whereas attempts to discern the −35 hexamer are virtually hopeless. Although the approximate position of transcriptional start site (TS) may be localized in this way, these guesses fail frequently and hexamers less similar to −10 consensus or unexpectedly close to the translational starts turn out to be the actual −10 regions" (page 315, col. 1, last paragraph). Hence Pátek et al., clearly underscores the significance of the main elements of a functional *C. glutamicum* promoters including the -10 element and -35 element. Additionally, it was well known in the art that patterns of single mutations in the promoter are critical to their structure/function relationship. The skilled artisan understands that one nucleotide change in a DNA molecule could result in the loss of its biological activity as demonstrated by lost of activity by mutagenesis of P-*dapA* promoter of *C. glutamicum (*Vasicová et al., *J. Bacteriol.* 1999, pp. 6188–6191). Mutations confirmed in mutational studies that $T_1$ and $T_6$ are the essential positions in −10 hexamer (e.g., the hexamer

$T_1A_2(T/G)_3A_4A_5T_6$)) and that the G at the second position upstream of the −10 is also vital. Mutation of the G at the second nt downstream of the −10, which was weakly conserved (43%), reduced also sharply the promoter activity. Moreover, the essentiality of the T tract in the positions −55 to −50 for P-*dapA* function was also confirmed (p. 6190, col. 1, paragraph 1, Fig. 3A). Additionally, promoter transcriptional activation is regulated upstream by several DNA-binding proteins recognizing distinct response elements. Moreover, transcription of a gene is further complicated by transcriptional regulatory complexes modulating elements outside the promoter gene and other factors including A+T-rich tract within the region -40 to -55 and regulatory stress factors such as heat shock, carbon substrate, starvation (Pátek et al., 2003, p. 315, col. 1 paragraph 1 and col. 2, paragraph 2). Thus, it is not possible from reading the examples in the specification as filed to envision what types of mutations have been introduced, how many nucleotides may be mutated and/or deleted within the expression unit comprising the nucleotide sequence of SEQ ID Nos. 1 and 2, wherein said nucleic acid molecule is functionally linked to a gene of interest to ensure transcription/ translation. Though the amplified DNA fragment from the sodA gene *of C. glutamicum* ATCC 13032 of approximately 620 base pairs in size comprising the nucleotides of SEQ ID Nos. 1 and 2 was used to generate the ATCC13032 Psod $lysC^{fbr}$ and ATCC 13032 pCLiK5MCS PSODmetA, this may not be sufficient, as the ordinary artisan would immediately recognize that active or binding sites in the promoter are affected by upstream promoter elements and other transcription regulatory elements including sequence length and other factors. Because the specification is silent about DNA-binding proteins regulating transcription by binding regulatory elements in the nucleic acid sequence SEQ. ID NO. 1 (e.g, represents the promoter sequence of Psod from the wild type *C.glutamicum*)

and the nucleic acid sequence SEQ. ID. NO. 2 (e.g., represents the nucleic acid sequence of the expression unit of Psod from C. glutamicum), any substitution (e.g., mutations, deletions) of nucleotide residues can often destroy the activity of the DNA promoter or prevent the generate promoter from exhibiting promoter activity. Neither prior art of record nor the as-filed specification provides sufficient guidance to enable a person skilled in the art to make and use a genus of fragments and/or variants of SEQ ID NO 1 and SEQ ID NO: 2 as broadly claimed.

As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other sequences embraced by the claim. This is the case here, where the specification discloses only one putative functional amplified DNA fragment from the sodA gene of *C. glutamicum* ATCC 13032 of approximately 620 base pairs in size comprising SEQ ID Nos. 1 and 2 that was used to generate the ATCC13032 Psod $lysC^{fbr}$ and ATCC 13032 pCLiK5MCS PSODmetA and provides no

guidance on determining which polynucleotide variants of the claimed expression unit comprising SEQ ID Nos. 1 and 2 would have be functional as promoters.

To put the situation in perspective, the number of possible polynucleotide sequences of 191 nucleotides in length (SEQ ID NO: 2 is 191) is $4^{191}$ (approx. $10^{114}$). The number of possible nucleotide sequences that are of a given % identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following expansion formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + ... + X^{n-1}L(L-1)(L-2)...(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)...(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be substituted relative to the reference sequence at a given % identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids). The $n^{th}$ term of the expansion can be rewritten as:

$$X^n \cdot {}^{L!}/_{n!\,(L-(n-1)!}$$

For a 191-residue nucleotide sequence that is at least 90% identical to a reference sequence of 191 nucleotides, e.g. SEQ ID NO: 2, the number of possible sequences having 19 nucleotide substitutions relative to the reference (the penultimate term of the formula) is approximately $4.6 \times 10^{32}$, whereas the number of possible sequences having 20 nucleotide substitutions relative to the reference (the final term of the formula) is approximately $1.2 \times 10^{34}$. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. Even claiming 99% identity does little to realistically improve the situation, as the same analysis

with SEQ ID NO: 2 using 99% homology (e.g., 2 substitutions) yields $8.1 \times 10^3$ possible variants. Also, as the number of permitted substitutions increases the number of possible variant sequences increases geometrically. While limiting the scope of potential sequences to those that are at least 90 or 99% identical to a reference, for example, greatly reduces the number of potential sequences to test, it does not do so in any meaningful way.

In terms of the structural requirements of the nucleic acid molecules, claims 2 and 4-7 recite an arbitrary structural relationship between the claimed nucleic acid sequence(s) and the single disclosed species of nucleotide sequence based upon hybridization of nucleic acid. Hybridization of two nucleic acids, even under high stringency conditions, requires only that the two nucleic acids share between 25 and 50 nucleotides in common. (Kennell, *Progr Nucleic Acid Res. Mol. Biol.* 11: 259-301, 1971, at the paragraph bridging pages 260-261). Thus such a sequence could have only 25 to 50 nucleotides in common out of the 173 nucleotides of SEQ ID No. 1 or 191 nucleotides of SEQ ID No. 2, wherein the fragments of 25 to 50 may not retain full or even partial promoter activity as the fragments are not required to have the promoter critical sites including, for example, two short sequences at -10 and -35 positions upstream from the transcription start site. Applicant has provided little or no guidance beyond the mere recitation of conditions for hybridization (page 13, liens 15-30).

As the result, given the unpredictability of the art and the lack of working example in the instant specification, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to practice the instant invention to identify an enormous number of expression units as broadly or generically claimed, with a resultant identification of a promoter region of the sodA gene of *C. glutamicum* ATCC 13032 comprising

SEQ ID Nos. 1 and 2 able to function as promoters to express a heterologous gene of interest in any host cell as broadly claimed.

***Claim Rejections - 35 USC § 103(a)***

The specification as filed at page 10, lines 20-25, provides a definition of "an expression unit" as "a nucleic acid having expression activity, i.e. a nucleic acid which, in functional linkage to a nucleic acid to be expressed, or gene, regulates the expression, i.e. the transcription and the translation of this nucleic acid or of this gene" . To the extent that claims 6 and 7 encompass an isolated nucleic acid comprising the promoter region of the *C. melassecola sodA* gene the full length of SEQ ID NO. 1 and SEQ ID No. 2 wherein the nucleic acid sequence is functionally linked to a nucleic acid sequence to ensure translation of ribonucleic acids, the following rejection applies.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Merkamm et al., (Journal of Bacteriology, 2001, pp. 1284-1295, of record) (SCORE Search Results Details for Application 10583191 and us-10-583-191-1,-2.rge, Results 12 and 9, respectively) in view of Merkamm et al.

Merkamm discloses the isolated nucleic acid of the *sodA* gene encoding the *Corynebacterium melassecola* manganese-cofactored superoxide dismutase (SOD) protein (p. 1284, col. 2). Merkamm illustrates in Fig. 3 the nucleotide sequence of *C. melassecola sodA* region comprising a promoter region with putative ribosome-binding sites (RBS, boxed), and conserved transcription factors binding sites for the RNA polymerase holoenzyme (e.g, ATTATT, underlined) (p. 1288, Fig. 3). Absent evidence to the contrary the sequences having the SEQ ID Nos. 1 and 2 are contained in the isolated nucleotide sequence of the *C. melassecola sodA* region. Additionally, Merkamm discloses that the *C. melassecola sodA* gene was cloned generating the pMM8 and expressed in *E. coli* under the control of an *E. coli trc* promoter. The cloned DNA fragment was tested for its ability to complement the QC1799 *sodA sodB* mutant of *E. coli* (p. 1286, col. 1, last paragraph). Conversely, the upstream sequence of the *sodA* gene (e.g., promoter) is contemplated for expression of a reporter gene (p. 1292, col. 1, paragraph 2). Introducing said construct into a host cell is implicitly anticipated for reporter gene expression (**Current claims 2, 6 and 7**). Therefore, in view of disclosure of the *sodA* gene encoding the *Corynebacterium melassecola* manganese-cofactored superoxide dismutase (SOD) protein mapping specific location of critical elements in the promoter sequence including the -10 element, -35 element and other transcriptional elements, it would have been *prima facie* obvious to one of ordinary skill in the art to use the sodA promoter for expression of an

heterologous gene, e.g., a reporter gene, in a host cell. One of ordinary skill in the art, at the time the invention was made, would have a reasonable expectation of success in using the sodA promoter functionally linked to a gene to ensure transcription of said gene in a host cell as the manipulation of previously identified DNA fragments and cell transformation systems is within the ordinary level of skill in the art of molecular biology.

***Provisional Rejection, Obviousness Type Double Patenting-***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2, 6 and 7 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 5 and 6 of copending Application No. 12/030575. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims and claims 2, 5 and 6 of the US Patent Application of copending Application No. 12/030575 are obvious variants because all claims are broadly drawn to :

An isolated nucleic acid molecule having promoter activity, selected from the group comprising,

A) a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1;

B) a nucleic acid molecule comprising a nucleotide sequence of at least 90% identity to the nucleotide sequence of SEQ ID NO: 1;

C) a nucleic acid molecule which hybridizes with the complement of the nucleotide sequence of SEQ ID NO: 1;

D) a nucleic acid molecule comprising a fragment of the nucleic acid molecule of (A), (B) or (C), wherein the molecule has promoter activity; wherein the nucleic acid molecule does not consist of SEQ ID NO: 1, and additionally comprising

an isolated nucleic acid molecule selected from the group consisting of:

E) a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 2;

F) a nucleic acid molecule comprising a nucleotide sequence of at least 90% identity to the nucleotide sequence of SEQ ID NO:2;

G) a nucleic acid molecule which hybridizes with the complement of the nucleotide sequence of SEQ ID NO:2; and

H) a nucleic acid molecule comprising a fragment of the nucleic acid molecule of (E), (F) or (G), wherein the molecule has expression activity; wherein the nucleic acid molecule does not consist of SEQ ID NO:2.

Claim 6 of the instant invention is drawn to an expression cassette comprising a nucleic acid whereas claim 5 of copending '575 is drawn to an isolated nucleic acid.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

## ***Conclusion***

Claims 2 and 6-7 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also

enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633